AWARD NUMBER: W81XWH-15-1-0288

TITLE: High Fidelity Drug Repurposing, Molecular Profiling, and Cell Reprogramming

PRINCIPAL INVESTIGATOR: Dr. Chris Albanese

CONTRACTING ORGANIZATION: Georgetown University
                                        Washington, DC 20057

REPORT DATE: September 2016

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
                        Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for Public Release;
                                      Distribution Unlimited

The views, opinions and/or findings contained in this report are those of the author(s) and should not be construed as an official Department of the Army position, policy or decision unless so designated by other documentation.

REPORT DOCUMENTATION PAGE

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
September 2016	Annual	1 Sep 2015 - 31 Aug 2016

4. TITLE AND SUBTITLE

High Fidelity Drug Repurposing, Molecular Profiling, and Cell Reprogramming

5a. CONTRACT NUMBER

5b. GRANT NUMBER
W81XWH-15-1-0288

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
Dr Chris Albanese

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

E-Mail:albanese@georgetown.edu

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

Georgetown University
37th & O Streets, NW
Washington, DC 20057-0001

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)

U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT

Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

To provide successful immediate-term treatment of PCa, and to prolong or prevent the need for androgen deprivation therapy and its lethal corollary, castrate resistant prostate cancer. We will integrate two paradigm-shifting Georgetown-Lombardi technologies (TMFS/network pharmacology and CRCs) to discover and test repurposed drugs that target PCa on an individual patient basis. ***Objective 1:*** We will enrich the FDA-approved drug database to include world-wide approved and experimental drugs and add new target structures as needed. ***Objective 2:*** TMFS will be applied to the molecular profiles derived from a series of *pten* mutant tumors from engineered mice and predicted drugs will be tested on conditionally reprogrammed cultures of these cells in vitro as well as in vivo as allografts. ***Objective 3:*** We will also complete the characterization of 10 human normal and prostate cancer CRC lines by Illumina bead array and RNAseq. ***Objective 4:*** These datasets will be interrogated for potential targets and repurposable drugs identified using TMFS. The drugs will be tested on prostate cells growth *in vitro* to calculate the LD50 in preparation for future studies in vivo.

15. SUBJECT TERMS

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON USAMRMC
a. REPORT	b. ABSTRACT	c. THIS PAGE			19b. TELEPHONE NUMBER (include area code)
Unclassified	Unclassified	Unclassified	Unclassified	6	

Table of Contents

Introduction

In 2012, we published three landmark papers. First, we used a novel computational modeling method of "Train, Match, Fit, Streamline" (TMFS) to predict alternative targets, i.e. "drug repurposing", for all FDA-approved and experimental drugs. We have recently integrated our proprietary TMFS with network pharmacology, which will help to further define and refine the drug-disease inferences generated by our modeling system. We also described a powerful new epithelial cell culture technique, yielding Conditionally Reprogrammed Cells, or CRCs, for the rapid and prolonged culturing of both normal and malignant prostate epithelium. Finally, we previously established that CRC approach could be rapidly (14 days) used for identifying a "repurposed" drug, vorinostat, for the successful treatment of a lethal case of recurrent respiratory papillomatosis. With support from the DOD we now have 7 matched sets of normal and malignant prostate cells growing as CRCs.

Our goal is to affect a paradigm shift in the way prostate cancer is treated. Indeed, despite radical primary therapy for curative intent, 30-35% of patients experience disease recurrence and few options exist for effective interdiction. To accomplish this goal we need better ways of identifying approved drugs, of validating the predicted target interactions and finally for applying these data to patient samples.

In this proposal we integrate two paradigm-shifting Georgetown-Lombardi technologies (TMFS/network pharmacology and CRCs) to discover and test repurposed drugs that target PCa on an individual patient basis. We will, for the first time, synergistically link our in silico approved-drug repurposing software and databases with our breakthrough CRC technology. This proposal promises to provide significant short- and long-term benefits to the research community and, ultimately, directly to patients. For example, while family history, PSA profile and an abnormal digital rectal exam are associated with more lethal cancers, there are no predictive biomarkers to guide optimal selection of a management strategy for an individual patient (e.g. active surveillance, radical prostatectomy, radiation or hormonal/chemo therapies).

CRCs are perfect for medium and high throughput drug screening, similar to what has been done for decades using transformed cell lines, only bringing the data to the bedside through the use of patient derived samples. Additionally, our novel TMFS system also brings an unparalleled level of accuracy and specificity to in silico identification of approved drugs and new targets.

By using repurposed drugs to delay, or perhaps even negate, the need for androgen depravation therapy (ADT) success with treating localized disease can be viewed as could be viewed as chemoprevention, as it is ADT that typically leads to castrate resistant PCa, and while we anticipate finding repurposed drugs for all stages of PCa, it is advantageous to avoid ADT as long as is possible for many biological and health reasons.

We anticipate that this combination of our TMFS and CRC technologies represent the future of a truly personalized approach to PCa research and patient treatment

Keywords

Drug repurposing, primary cell, conditionally reprogrammed cells. localized prostate cancer, androgen independent prostate cancer, network pharmacology

Accomplishments

To date 2 matched pairs of normal prostate and prostate cancer CRCs have undergone molecular profiling by Illumina bead array. The samples came from Gleason 7 and Gleason 8 patients and the data analyzed based on the differences in expression between the normal and tumor cells. The microarray data were processed by TMFS and over a dozen FDA approved and experimental drugs were identified. Some of the tops scoring "hits" were already in clinical

trials, and these were excluded for the time being. Other hits were similar between the 2 patients and these hits included Sulforathane (SFN) and Phenethyl Isothiocyanate (PEITC). Dose response curves were performed and the EC 50's for normal and tumor lines were established. As seen in Fig 1, in both patients 1 and 2, the tumor cells were significantly more sensitive to the

Fig 1
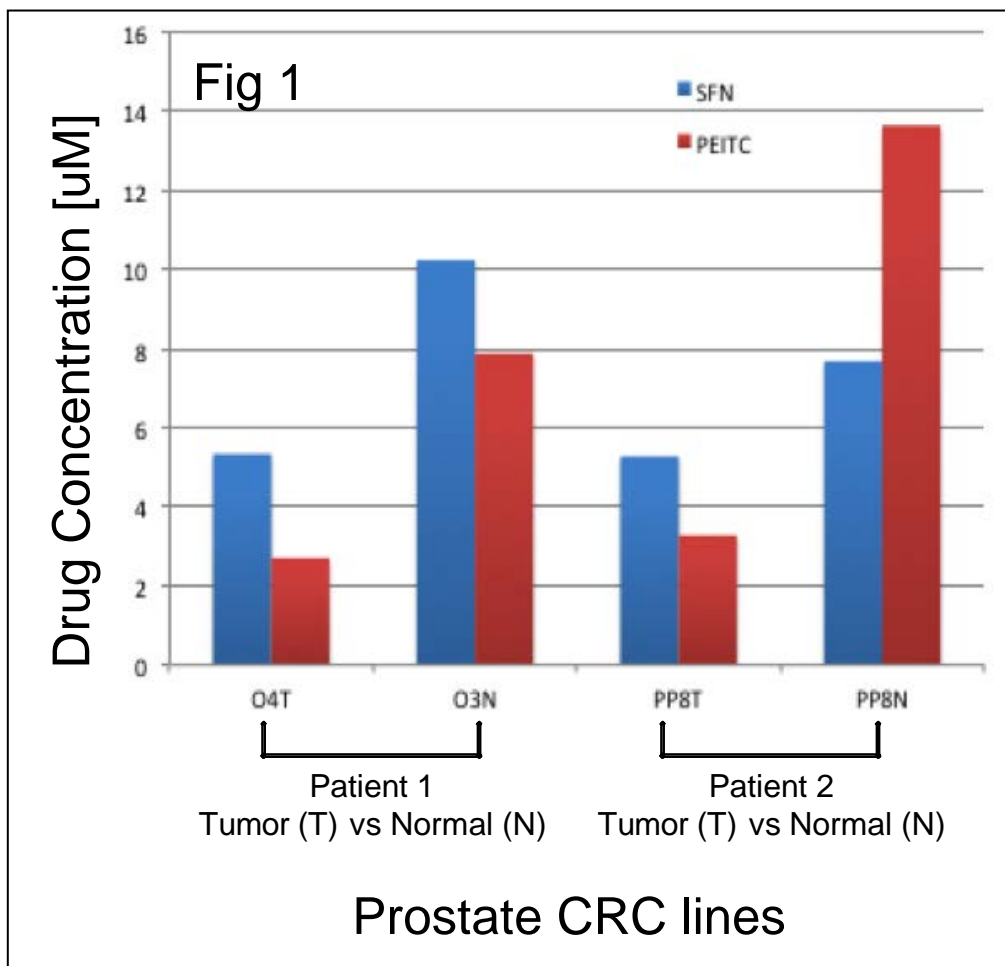
compounds than the matched normal cells, as predicted by TMFS. Additional drugs are being tested in these 2 lines. In addition we are using both TMFS and standard molecular techniques to identify the key target responsible for the heightened drug sensitivity in the cancer cells. These data form the beginnings of a manuscript.

Additional human CRC lines (normal and malignant) will be interrogated and tested in the same manner.

For the mouse studies, the animal colony has been expanded as required and the analyses by MRI have begun. The goals are to identify animals with prostate tumors. Once identified, the tumors will be collected (as will prostates from normal mice), CRCs will be generated and drugs identified by TMFS as above.

Impact
Collectively, our new findings strongly suggest that the CRC and TMFS innovations synergize to give broad applicability in both rapidly identifying approved drugs and testing their efficacy in a personalized approach to patient treatment. We firmly believe that the CRC technology in combination with our TMFS computational modeling software and database represents the future of personalized/precision prostate cancer research and treatment.

Changes/Problems
None

Products
None

Participants & Other Collaborating Organizations

Dr. Chris Albanese
Dr. Stephen Byers
Dr. Siva Daksanamurthy
Dr. Olga Rodriguez
Dr. Lucas Tricoli
    All at Georgeotwn University Medical Center, Washington DC

Special Reporting Requirements
None
Appendices
None